Spindle Activity in Children During Cardiac Surgery and Hypothermic Cardiopulmonary Bypass

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Abstract: Hypothermia has marked effects on the electrical activity of the brain, which has been shown in animals as well as in humans. The aim of this study was to investigate EEG spindle activity in children during cardiac surgery and hypothermic cardiopulmonary bypass. The authors obtained intraoperative 21-channel EEG recordings in 36 children (mean age, 22 months; range, 6 days to 69 months) with congenital heart disease. Bipolar EEG derivations were analyzed visually for rhythmic spindle activity based on morphology, frequency, duration, and amplitude. Linear regression analysis for duration, frequency, and amplitude versus rectal temperature was performed in each individual. Spindle activity was observed in 17 children (16 children < 12 months of age). Progressive slowing of spindle frequency with decreasing rectal temperature was found (mean decrease, 0.54 +/- 0.31 Hz/ degrees C). Spindle duration increased on average by 0.69 +/- 0.39 second/ degrees C during cooling procedures. Spindle amplitude did not show any correlation to changes in rectal temperature. The current study demonstrates spindle activity during hypothermic cardiopulmonary bypass with temperature-dependent spindle modifications of frequency and duration. Although the temperature-dependent changes in this study confirm temperature coefficients of other EEG studies, the reasons for the clear age relationship and the "nature" of these spindles remain unknown.

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Spindle Activity in Children During Cardiac Surgery and Hypothermic Cardiopulmonary Bypass

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Summary: Hypothermia has marked effects on the electrical activity of the brain, which has been shown in animals as well as in humans. The aim of this study was to investigate EEG spindle activity in children during cardiac surgery and hypothermic cardiopulmonary bypass. The authors obtained intraoperative 21-channel EEG recordings in 36 children (mean age, 22 months; range, 6 days to 69 months) with congenital heart disease. Bipolar EEG derivations were analyzed visually for rhythmic spindle activity based on morphology, frequency, duration, and amplitude. Linear regression analysis for duration, frequency, and amplitude versus rectal temperature was performed in each individual. Spindle activity was observed in 17 children (16 children $<$ 12 months of age). Progressive slowing of spindle frequency with decreasing rectal temperature was found (mean decrease, 0.54 $\pm$ 0.31 Hz/°C). Spindle duration increased on average by 0.69 $\pm$ 0.39 second/°C during cooling procedures. Spindle amplitude did not show any correlation to changes in rectal temperature. The current study demonstrates spindle activity during hypothermic cardiopulmonary bypass with temperature-dependent spindle modifications of frequency and duration. Although the temperature-dependent changes in this study confirm temperature coefficients of other EEG studies, the reasons for the clear age relationship and the "nature" of these spindles remain unknown. **Key Words:** Spindle activity—Hypothermia—Children—Cardiopulmonary bypass—Cardiac surgery—EEG.

Systemic hypothermia is used commonly to protect cerebral function during cardiopulmonary bypass. Although the effects of hypothermia on brain electrical activity have been studied extensively (Hicks and Poole, 1981; Mizrahi et al., 1989; Reilly et al., 1974; Salerno et al., 1978; Weiss et al., 1975), spindle activity during hypothermia has been described sparsely (Akiyama et al., 2001; Cohen et al., 1977). In a pilot study for the investigation of new neuroprotective strategies in children undergoing cardiac surgery with hypothermic cardiopulmonary bypass (HCPB), the intraoperative EEG monitoring of some patients revealed a pronounced spindle activity with progressive slowing of frequency during cooling procedures. The aim of this work was to describe and to investigate this spindle activity during HCPB in more detail.

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METHODS

Patients

Intraoperative multichannel EEG recordings during HCPB were performed in 36 children with congenital heart disease (mean age, 22 months; range, 6 days to 69 months). Thirteen children were part of a placebo-controlled study with dextromethorphan (Schmitt et al., 1997) and 23 children participated in a pilot study for the investigation of intra- and postoperative EEG changes and of systemic oxidative stress parameters. Children with associated noncardiac malformations or neurologic abnormalities were not included in this study. Written informed consent was obtained from the parents of the children and both studies were approved by the ethical committee of the University Children's Hospital, Zurich.

Anesthetic and Cardiopulmonary Bypass Procedures

Premedication was oral midazolam (0.4 mg/kg). Anesthesia was induced with halothane (0.5 to 1.5 vol%) or sevoflurane (3 to 8 vol%), nitrous oxide, oxygen (fraction inspiratory oxygen concentration, 0.5), and pancuronium (0.1 mg/kg). After endotracheal intubation, anesthesia was supplemented with flunitrazepam or midazolam and fentanyl or sufentanil, and the patients were ventilated with a mixture of oxygen and air (fraction inspiratory oxygen concentration, 0.5 to 1.0). During mechanical ventilation, halothane was equilibrated to 0.4 to 0.8% and sevoflurane to 0.5 to 2.0% end-tidal concentration. At the beginning and during HCPB, maintenance of anesthesia was performed with flunitrazepam 0.05 mg/kg and fentanyl 20 μg/kg (halothane group) or with midazolam 0.15 μg/kg/hour and sufentanil 0.9 to 1.8 μg/kg/hour (sevoflurane group). Relaxation was repeated only at the beginning of HCPB with half the initial dose (0.05 mg/kg pancuronium). Hypothermic cardiopulmonary bypass was performed with a roller pump, a membrane oxygenator, and an arterial filter. Perfusion rate was 100 to 130 mL/kg/min or 150 to 200 mL/kg/min during normothermia, and pump flow was reduced gradually as temperature decreased. Alpha stat acid–base management was used and adequacy of pump flow was monitored by intermittent determination of arterial and venous oxygen saturation. In all children with body weight $\leq$ 8 kg, prednisolone (30 mg/kg) was added to the priming solution of the HCPB circuit. Six children were treated with dextromethorphan (Schmitt et al., 1997).

EEG Recording and Analysis

EEG recordings were obtained on a 21-channel standard system (IT-med, Germany). The EEG signals were amplified (time constant, 0.3 second), on-line analog-to-digital converted (sampling rate, 128 Hz; resolution, 12 bit), digitally filtered (high-frequency filter, 70 Hz), and stored on optical disks. Intraoperative recording started after intubation and was continued until the end of the operation. Surgical and anesthetic procedures, cardiorespiratory parameters, and body temperature (rectal [$°C_{rt}$]) were documented periodically.

Bipolar EEG derivations (F3-C3, C3-P3 and F4-C4, C4-P4; International 10-20 System) were analyzed visually for rhythmic spindle activity based on morphology (waxing and waning component), frequency, amplitude, and duration. The visual analysis was performed using a ruler displayed on the computer screen (IT med software tool, Germany; Fig. 1). Frequency, duration, and amplitude were determined in 0.5 $°C_{rt}$ temperature intervals during cooling and in 1 $°C_{rt}$ intervals during rewarming. Peak-to-peak amplitude was measured at the wave with highest amplitude. The waxing spindle onset and waning offset were difficult to determine and only allowed an approximate calculation of the spindle duration. Spindle end points were chosen where the predominant frequency changes, the spindle morphology disappears, and the spindle amplitude becomes more like nonspindle background. To reduce the error rate, we calculated mean values of frequency, duration, and amplitude of two to five spindles (5 spindles in 106 of 133 values) for all documented temperature intervals of each individual. Additionally, the visual analysis was performed entirely by the same experienced electroencephalographer (B.S.).

Statistics

Linear regression analysis (slope, intercept at 38 $°C_{rt}$, and correlation coefficients) of duration, frequency, and amplitude versus rectal temperature was performed for each individual. Mean data are presented (mean correlation coefficients after Fisher's z transformation) in Table 1.

RESULTS

Rhythmic spindle activity was observed in 17 children (16 children age 16 days to 11 months and 1 child age 18 months). No spindle activity could be detected in a 6-day-old child and in 18 children age 12 to 69 months. Only four children showed spindle activity before the cooling procedure started. The spindles were comparable with those at equivalent temperatures during early HCPB and were not used for further analysis. Two children showed spindles during rewarming only. Three children with spindle activity (each younger than 10 months of age) and three without (each older than 12 months of age) received dextromethorphan.

Three children had to be excluded from further analysis because of insufficient temperature documentation during HCPB (less than four documented temperature intervals). Table 1 shows the relationship between rectal

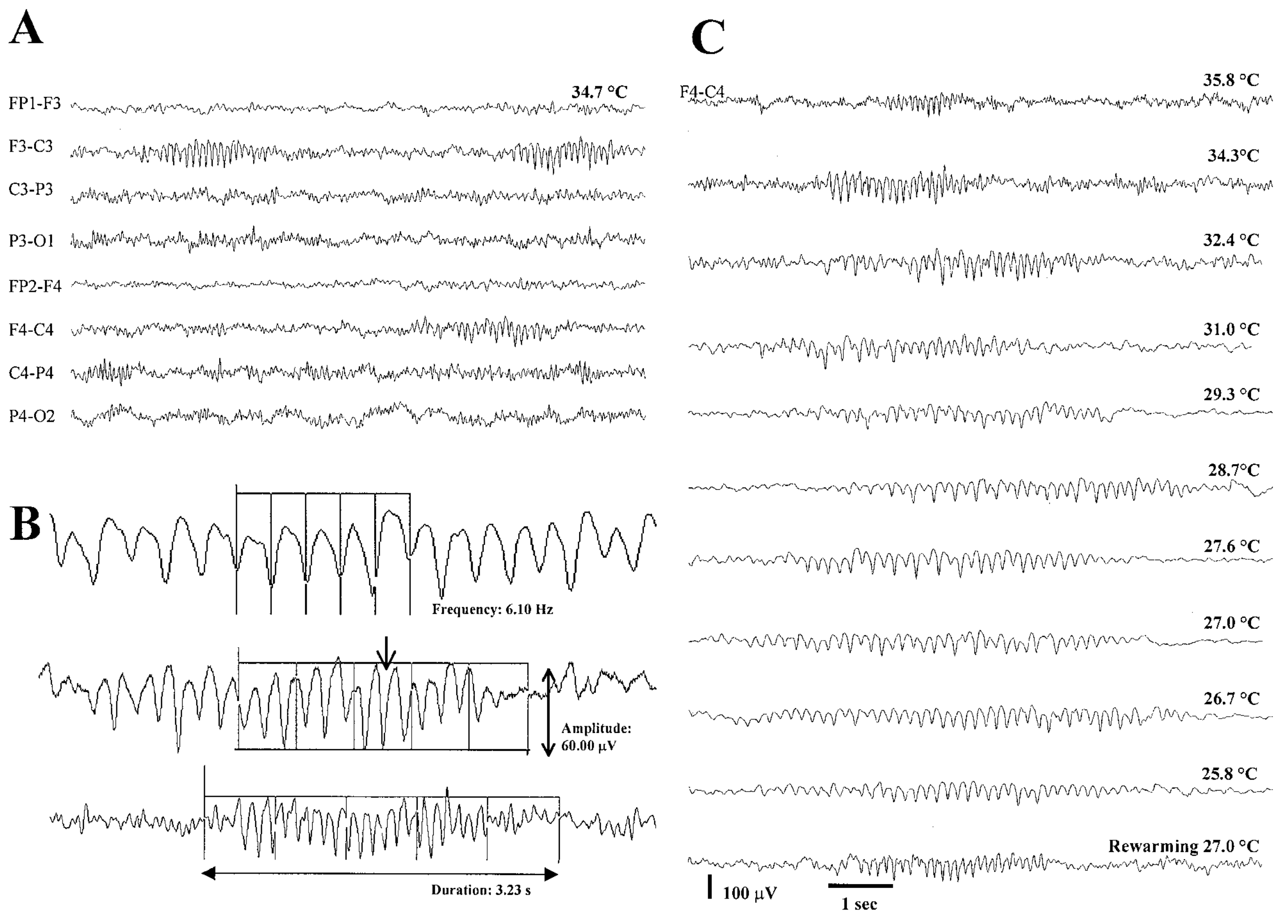

FIG. 1. (A) Detail from the EEG tracings of a 8-month-old boy (patient no. 6) during hypothermic cardiopulmonary bypass: spindle activity with a spiky negative component, a rounded positive component, and a shifting asymmetry between both hemispheres. Continuous background activity in the β range. **(B)** Determination of frequency (five ruler divisions, each dividing line at the bottom of five consecutive waves), peak-to-peak amplitude (y-extension of the ruler) of the highest wave and duration (interval from the first and to the last ruler division) using the measuring tool of IT med. **(C)** Changes of spindle activity (morphology, frequency, and duration) in a 9-month-old boy (patient no. 10) during cooling and rewarming.

temperature, spindle frequency, and duration in the remaining children (n = 12). Progressive slowing of spindle frequency with decreasing rectal temperature was found (mean decrease, 0.54 ± 0.31 Hz/°C_{rt}). The mean spindle frequency intercept at 38 °C_{rt} was at 10.24 ± 1.52 Hz. However, intercept values may not reflect the true spindle frequencies at 38 °C_{rt} because frequency may decrease very rapidly when body temperature drops initially from 38 °C_{rt} to 35°C_{rt} (Figs. 2 and 3). In addition, spindle duration increased by 0.69 ± 0.39 second/°C_{rt} during cooling procedures, but the correlation was weaker compared with spindle frequency (mean $r^2 = 0.88$ for duration vs. mean $r^2 = 0.94$ for frequency). Spindle amplitude did not show any correlation to decreasing rectal temperature during HCPB (range at 33 °C_{rt}, 19 to 193 μV).

In contrast to cooling, the rewarming procedure showed a reverse effect on spindle frequency and duration (see Fig. 2, child no. 10). However, insufficient documentation of rectal temperature resulting from individually different time rates for rewarming made statistical analysis unreliable.

DISCUSSION

In this report, a decrease of spindle frequency and an increase of spindle duration during progressive cooling was demonstrated in children during HCPB. To our knowledge, this is the first report in human subjects investigating large hypothermic effects on spindle activity. However, it is important to note that these findings could be shown almost exclusively in children younger than 12 months of age, which may explain the lack of available reports so far. The morphology (spiky negative

TABLE 1. *Temperature dependence of spindle frequency and duration during cooling*

Patient no.	Age, ms	n	Temperature versus frequency: Slope, Hz/°C_{rt}	Intercept, Hz 38 °C_{rt}	r^2	Temperature versus duration: Slope, (second/°C_{rt})	Intercept, (second) 38 °C_{rt}	r^2
1	1	6	0.38	8.26	0.98**	−1.45	−0.90	0.85**
2	2	6	0.61	10.90	0.95**	0.02	5.51	0 (ns)
3	2	10	0.47	9.39	0.98**	−0.87	4.79	0.47 (ns)
4	2	4	0.35	7.88	0.69 (ns)	0.99	18.19	0.98**+
5	4	6	1.28	12.10	0.88**	−1.18	1.72	0.91**
6	8	8	0.85	11.69	0.72**	−0.79	1.04	0.89*
7	9	9	0.58	10.44	0.83**	−0.25	2.41	0.59*
8	9	7	0.13	8.82	0.67*	−0.40	1.61	0.90**
9	9	7	0.57	11.58	0.89**	−0.44	1.07	0.66*
10	9	12	0.60	11.66	0.86**	−0.67	1.26	0.95**
11	10	5	0.11	8.81	0.65*	−0.18	4.16	0.25 (ns)
12	11	4	0.60	11.40	0.88 (ns)	−0.55	0.48	0.52 (ns)
mean			0.54	10.24	0.94	−0.69	3.44	0.88
std			0.31	1.52	0.49	0.39	3.84	0.63

regression equation coefficients (slope and intercept at 38 °C_{rt}) and correlation coefficients r^2 are presented for individual infants (n = 12). Mean intercepts (38 °C_{rt}), slopes, and correlation coefficients (after Fisher's z transformation and back transformation) were calculated for frequency and duration.

n, number of data points; ** $p < 0.01$ and * $p < 0.05$, $^+$positive correlation (not included in mean calculations).

ns, not significant; std, standard deviation.

component and rounded positive component) and the frequent shifting asymmetries between both hemispheres may resemble the characteristics of sleep spindles during the first year of life. Sleep spindles are short-lasting rhythmic EEG waves in the frequency range of approximately 12 to 14 Hz and are characterized by a waxing and waning oscillatory component. They are generated in the thalamus as a result of synaptic interactions and intrinsic membrane properties of inhibitory neurons of the reticular thalamic nucleus and excitatory thalamocortical cells (Steriade et al., 1993). Sleep spindles appear before the age of 2 months and increase in duration and amplitude between 3 and 9 months of age (Jankel and Niedermeyer, 1985; Louis et al., 1992; Tanguay et al., 1975). This age-related spindle enhancement during the first year after birth may reflect maturational processes

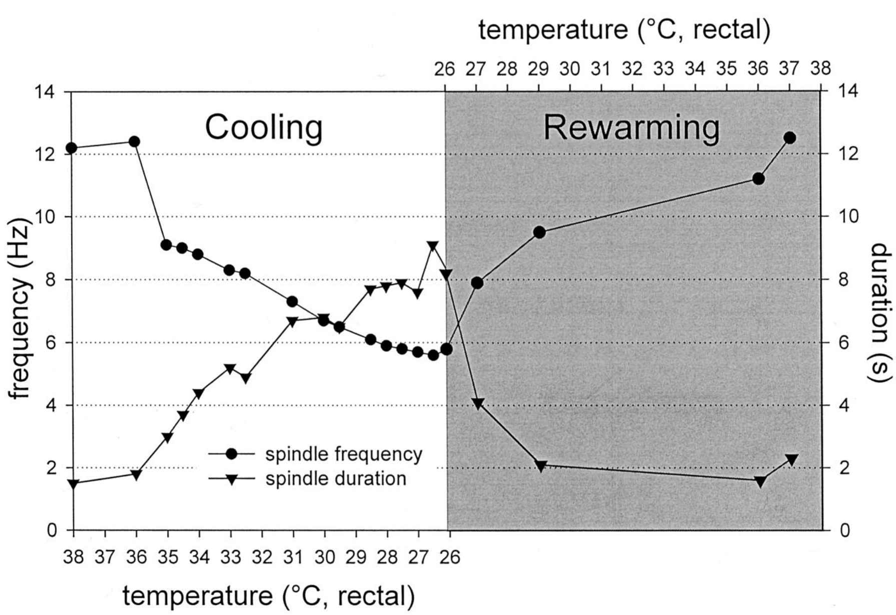

FIG. 2. Temperature-dependent changes of spindle frequency and duration in an individual child (patient no. 10).

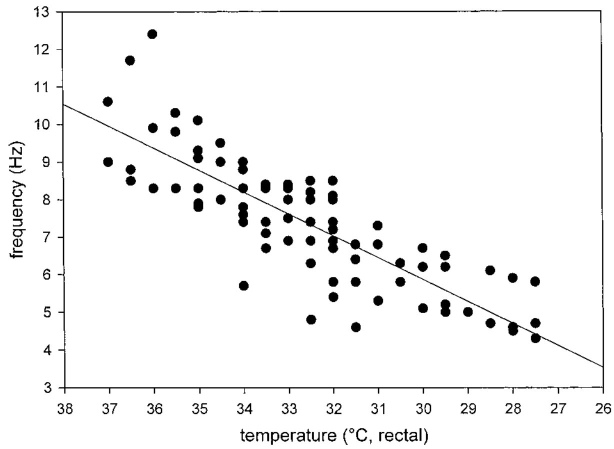

FIG. 3. Decrease of spindle frequency during cooling in hypothermic cardiopulmonary bypass. Pooled data of 12 infants with a regression line presented (pooled intercept at 38 °C_{rt}, 10.53 Hz; pooled slope, 0.58 Hz/°C_{rt}; $r^2 = 0.69$, $P < 0.01$).

of the spindle-generating thalamocortical network (changing ionic conductance and intrinsic electrophysiologic properties) and may be responsible for easier visual identification in the EEG. However, with respect to the condition of general anesthesia in the studied children, a relationship of the observed spindle activity and sleep spindles remains speculative.

Spindlelike trains are produced by various pharmacologic agents such as barbiturates, nonbarbiturate sedatives, and benzodiazepines. This EEG activity is generally in the 14 to 30-Hz range (Jankel and Niedermeyer, 1985; Wauquier, 1999). In addition, several anesthetic drugs show a characteristic EEG pattern with anterior maximum in the β or α frequency range. We also observed continuous, more generalized β activity in our patients that, however, could be distinguished clearly from the phasic comblike spindle activity observed over the central leads (see Fig. 1).

A variety of drugs effect spindle density directly in humans (Hirshkowitz et al., 1982). Benzodiazepines and halogenated inhalational agents are agonistic modulators of the γ-aminobutyric acid $(GABA)_A$ receptors (Nishikawa et al., 2002) and increase the number of spindles (Hirshkowitz et al., 1982; Johnson et al., 1976; Keifer et al., 1996). The depth of anesthesia was comparable in all children and could, therefore, not explain sufficiently the exclusive occurrence at less than 12 months of age. From *in vitro* and *in vivo* studies, it appears that GABA activity is most pronounced during early developmental periods (Schousboe et al., 2001). In a positron emission tomographic study of epileptic children, the density of $GABA_A$ receptors showed the highest values at the age of 2 years, the youngest age studied (Chugani, 2001). It could well be that the elevated $GABA_A$ receptor density during early postnatal development may contribute to age-related enhancement of spindle activity in our study. Dextromethorphan had no influence on the occurrence of spindle activity because no difference could be detected between the treated children and the remaining group.

The intraoperative situation may produce several sources of artifacts expected as reproducible EEG phenomena with constant temporal and topographic distribution in the EEG. We were not able to identify any extracerebral source that may produce artifacts of slowing spindle frequency and increasing spindle length showing frequent shifting asymmetries during operative procedures.

Spindle activity was predominant during cooling and rewarming. Cohen et al. (1977) found fast spindle activity occurring in 3-month-old children decreasing to 9 to 10 Hz during cooling. Recently, an EEG pattern composed of 10 to 100 μV and 2 to 12-Hz waves lasting 3 to 6 seconds has been reported during hypothermia (Akiyama et al., 2001). With reference to our data, it remains unclear whether the hypothermia itself or the rapid shifting of temperature facilitated the occurrence of spindles. Rapid temperature changes were suggested to cause epileptiform activity in the EEG (Reilly et al., 1974) and to increase amplitudes in brainstem acoustic evoked potentials (Janssen et al., 1991). A temporary increase in cell membrane resistance after temperature shifting was discussed to result in larger spikes once cells have exceeded the firing threshold (Janssen et al., 1991).

Several animal and human studies have addressed the effects of temperature variations on the sleep EEG (for review see Deboer [1998]). However, data of EEG alterations by large temperature changes during hypothermia in humans have been limited. In reptilians, a linear regression between spindle peak frequencies and temperature was obtained ranging from less than 5 Hz at 5 °C to more than 30 Hz at 35 °C (De Vera et al., 1994). In a simulation of the EEG effects of a moderate temperature decrease in humans, a large increase of relative EEG power at 12 Hz and a large decrease at 15 Hz was demonstrated during nonrapid eye movement sleep (Deboer, 1998). In Djungarian hamsters Deboer and Tobler (1995) obtained a temperature coefficient of 2.5, which is in the range for most biologic processes, and suggested that the temperature dependence of the Na^+–K^+ pump is the rate-limiting step in synchronous neuronal cell firing during sleep. Therefore, with this coefficient a change in brain temperature of 1 °C is sufficient to shift EEG frequencies above 10 Hz by 1 Hz (Deboer, 1998). Because of individual temperature intervals and different numbers of data points in each subject, we were not able to provide temperature coefficients. However, performing linear regression analysis in all individuals, we observed a mean frequency shift of 0.54 Hz per 1 $°C_{rt}$ temperature change, which is in accordance with previous reports (Deboer, 1998).

Our inability to provide brain temperature for comparison with animal experiments is admittedly an important limitation of this study. Rectal temperature may include a considerable error rate in the calculation of the frequency shift because it does not reflect brain temperature accurately during rapid systemic cooling. Body size and the kinetics of cooling substantially affect the coherence of rectal and brain temperature. During active cooling procedures by HCPB, brain temperature may be lower than rectal temperature and the reverse may be the case on active rewarming. Therefore, spindle frequency may show different values at the same rectal temperature during cooling and rewarming.

However, this report raises more questions than gives answers. The spindle activity occurring almost exclusively in children younger than 12 months of age seems to be facilitated by hypothermia or rapid temperature changes. The spindles showed temperature-dependent modifications of frequency and duration. Although the temperature-dependent changes in our study confirm temperature coefficients of other EEG studies, the reasons for the clear age relationship and the "nature" of these spindles remain unknown. The striking resemblance to natural sleep spindles indicates their origin in thalamocortical circuits, possibly enhanced by anesthetic drugs. Spindle oscillations induce Ca^{++} entry into activated thalamic and cortical neurons and may lead to long-term changes of neuronal networks (Sejnowski and Destexhe, 2000). It would be important to know whether such mechanisms take place during hypothermia and which implications they have for the immature brain.

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